REMARKS

Examiner Interview

The undersigned confirms having met with Examiners Crowder and Gambel in the Examiner Interview on April 4, 2007, and thank the examiners for the courtesies extended in that interview. According to MPEP Section 713.04, a discussion of the substance of the interview is provided below.

Amendments

Claim 21 added herein finds support in the specification on page 28, lines 20 and 28-30. No new matter is added by this claim.

Section 102(e)

According to the Advisory Action dated January 22, 2007, the Section 102 rejection over US Patent 6,528,624 ("the '624 patent") is maintained. The Examiner acknowledges that the position 334 substitution was disclosed as having "little or no effect on C1q binding or complement activation" in the '624 patent, but maintains that such patent still anticipates claims 19 and 20 "for the reasons of record."

As to claim 19, the Examiner further states that it 'does not recite specific positions of the Fc region and the functional limitation being claimed is "antibody-dependent cell-mediated cytotoxicity (ADCC)" not C1q binding or complement activation.' The Examiner then goes on to reason that given that the '624 patent teaches a method of making and using a variant of a parent antibody which binds CD20 comprising amino acid substitutions in the Fc region (*e.g.* position 334, column 4 and 40 in particular), the prior art antibody would inherently have taught the claimed functional limitation of mediating "antibody-dependent cell-mediated cytotoxicity (ADCC) in the presence of human effector cells more effectively."

First, Applicants confirm their understanding from the interview that the rejection will not be maintained with respect to claim 20, which recites that the "variant comprises a variant human

IgG1 Fc region comprising substitutions at positions 298, 333 and 334 thereof." The Office has not explained where such variant is disclosed in the '624 patent.

Second, Applicants explained at the interview that the '624 patent is not available for "obviousness" purposes, since 35 USC Section 103(c)(1) excludes such subject matter, which was owned by the same person or subject to an obligation of assignment to the same person (Genentech) at the time the claimed invention was made. See assignment, Reel/Frame 010031/0041, related to USSN 09/282,846, which issued as the '624 patent. Applicants further explained that subject matter in the '624 patent that was not included in provisional application no. 60/080,447 filed April 2, 1998 ("the '447 provisional application") is not available even for "novelty" purposes under 35 USC Section 102(e). Applicants pointed out at the interview that the Office had not meet its burden of proving that the disclosure in the '447 provisional application anticipates claims 19 or 20 herein.

In the advisory action, the Examiner refers to column 4 and 40 of the '624 patent in maintaining the rejection of claim 19. Applicants submit that such disclosure in the '624 patent, to the extent it is supported by the '447 provisional application, does not anticipate claim 19 (much less claim 20) herein. In particular, column 4 of the '624 patent refers to Fc mutants comprising substitution(s) at amino acid position 270 or 329, or at two or more of amino acid positions 270, 322, 329, and 331.

Applicants reply that therapy with a CD20 antibody which mediates ADCC in the presence of human effector cells more effectively than the parent antibody is not disclosed in column 40 of the '624 patent. Lines 52-55 in column 40 of the '624 patent reads:

> "Mutants constructed, K274A, N276A, Y278A, S324A, P329A, P331A, *K334A*, and T335A, were assessed for their ability to bind C1q and also to activate complement. Many of these substitutions had *little or no effect on C1q binding or complement activation.* In the above assays, the P329A and

the P331A mutants did not activate complement and had decreased binding to C1q." (Emphasis added).

Example 2 in the '624 patent concludes that "the C1q binding epicenter of human IgG1 is centered around K322, P329 and P331." (Column 41, lines 16-18).

Applicants understand it is the disclosure of the K334A mutant in column 40 upon which the Examiner relies in maintaining the Section 102(e) rejection on the basis that such mutant would "inherently" have increased ADCC. Applicants respectfully disagree that such is an appropriate rejection of the present method claims. As explained at the interview, claim 19 (and claim 20) herein concern a "*method for treating lymphoma or leukemia in a mammal* comprising administering to the mammal a therapeutically effective amount of a variant of a parent antibody which binds CD20...", as opposed to the *antibody variant composition of matter*. Applicants submit that the disclosure of the K334A in column 40 when read in light of the '447 provisional application's overall guidance to treat a mammal suffering from a disorder by administering thereto a variant which "does not activate complement" (see, '447 provisional application, claim 16, for example) would not have described to the skilled person the inclusion of the K334A mutant in the therapeutic method. Rather, the skilled person would not have used K334A according to the '447 provisional application's teachings, since this variant had little or no effect on complement activation. Thus, the disclosure of the '447 provisional application would not have expressly disclosed the method of claim 19 herein. Therefore, the *therapeutic method* of claim 19 herein is not anticipated by the disclosure of the '447 provisional application.

In addition, bearing in mind that the rejection is a "anticipation" rejection, Applicants note that claim 19 herein recites "lymphoma or leukemia" which is a subgenus of "cancer" as disclosed in column 34, lines 66-67 of the '624 patent. Since the '624 patent does not recite "lymphoma or leukemia," this is yet another reason why claim 19 is not *anticipated* by the '624 disclosure.

Reconsideration and withdrawal of the Section 102(e) rejection is respectfully requested in view of the above.

Section 112, first paragraph, enablement

Claims 19 and 20 are rejected under 35 USC Section 112, first paragraph as failing to comply with the enablement requirement.

In the January 22, 2007 advisory action, the Examiner urges that the previously raised Section 112, first paragraph rejection is maintained for the reasons of record. The Examiner further explains that 'independent claim 19 recites "at least one amino acid modification" without setting forth specific amino acid residues and specific positions in the Fc region' and that as such, it is not clear what position in the Fc region of the anti-CD20 antibody can be modified to achieve the claimed function of mediating ADCC in the presence of human effector cells more effectively so that the antibody maintains its activity.

The Examiner continues to rely on Eccles as well as Tutt *et al.* for the proposition that even the data from *in vivo* animal experiments allegedly do not translate to therapeutic effect in heterogeneous human cancer patients.

Applicants respectfully traverse the rejection.

Applicants discussed the maintained "enablement" rejection at the interview. Applicants understand that the enablement rejection has two aspects. First, whether the claimed variants will be therapeutically effective. Second, whether the specification enables variants with improved ADCC function comprising "at least one amino acid modification" without setting forth specific amino acid residues and specific positions in the Fc region. Each of these aspects of the rejection will be addressed below.

As to the first aspect, whether the variants are therapeutically effective, Applicants explained at the interview that evidence has been provided demonstrating the *in vivo* efficacy of the claimed variants. In particular, Applicants directed the Examiner's attention to the published US patent

publication, US2006/0246004 A1, which described various CD20 antibody Fc variants with improved ADCC function (Examples 3, 6, and 12-13), including 2H7.v31, 2H7.v511, and 2H7.v114. Such variants were shown to be effective at B-cell depletion in mammals, see Examples 9, 15-16, and 18-19. Applicants disagree that Eccles or Tutt *et al.* would show that the data from the experiments in the published US patent application will not translate to therapeutic effectiveness in humans. Rather, Applicants submit that both Eccles and Tutt *et al.*, by recognizing that the CD20 antibody RITUXAN® is therapeutically effective in humans, support the enablement of the present claims, since that CD20 antibody product was validated in preclinical B-cell depletion studies of the type disclosed in US2006/0246004 A1. In other words, the evidence in its totality indicates that the positive B-cell depletion data *will* translate to therapeutic effectiveness in humans. Given such evidence, the Examiners indicated in the interview that this basis of the rejection was unlikely to be maintained.

Turning now to the second aspect of the rejection, related to the language "at least one amino acid modification," Applicants first note that this should not apply to claim 20. As to claim 19, Applicants pointed out at the interview that the present application discloses, for the first time, how to make and identify antibody variants with improved ADCC function. This is a pioneering invention worthy of claim scope commensurate with the important contribution to the field. Morever, while the preferred embodiment is a 298/333/334 variant, many Fc region residues are identified which can be modified to generate ADCC-improved variants. See Example 4 on pages 70- 89. The residues which can be altered to improve ADCC include: 256, 290, 298, 312, 326, 330, 333, 334, 360, 378, and 430 (see specification, page 28, lines 29-30, for example). Thus, the specification contains numerous working examples of variants comprising at least one amino acid modification. Moreover, the specification provides ample guidance on how to make variants comprising at least one modification and also how to screen for improved ADCC function either directly (specification, page 34, lines 9-14 and Example 4, by way of example) or indirectly via evaluating FcγR binding (specification, page 34, lines 3-8, page 35, line 25 through page 37, line 12, Examples 1 and 4, for instance). Thus, the skilled person, following the teachings of the present application, can practice the claimed invention across its scope insofar as

many different CD20 antibody Fc variants can be made and identified with the claimed improved ADCC function. Finally, Applicants explained that there is precedent for the Patent Office to recognize the important contribution of the present invention by granting claims that do not necessarily recite specific amino acid residues and positions in the Fc region (*e.g.* claim 1 of US Patent No. 6,737,056). For any and all of these reasons, Applicants submit that the second basis of the enablement rejection is addressed and the rejection should be withdrawn.

Thus, Applicants submit that the Section 112, first paragraph rejection of claim 19, and of claim 20 insofar as such is still maintained, should be reconsidered and withdrawn.

Applicants believe that this application is now in condition for allowance, and look forward to early notification to that effect.

Respectfully submitted,

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